General

Guideline Title

(1) American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. (2) Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. (3) Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline update on ovarian suppression.

Bibliographic Source(s)

Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update on ovarian suppression. J Clin Oncol. 2016 May 10;34(14):1689-701. [19 references] PubMed

Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Malin J, Mamounas EP, Rowden D, Solky AJ, Sowers MR, Stearns V, Winer EP, Somerfield MR, Griggs JJ, American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol. 2010 Aug 10;28(23):3784-96. [124 references] PubMed

Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Rowden D, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol. 2014 Jul 20;32(21):2255-69. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence-based, Formal Consensus, Informal Consensus, No Recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC) and the American Society of Clinical Oncology (ASCO): In 2016, ASCO performed a focused update of the 2014 guideline on adjuvant endocrine therapy based on emerging data concerning the benefits and risks of ovarian suppression in addition to standard adjuvant therapy in premenopausal women with estrogen receptor–positive breast cancer. The updated

recommendations are presented below, followed by the recommendations from the 2014 and 2010 guidelines that remain unchanged.

2016 Recommendations

Clinical Question 1

Should premenopausal women with estrogen receptor (ER)–positive tumors receive adjuvant ovarian suppression in addition to standard adjuvant therapy and, if so, in which subsets of patients?

Recommendation 1.1. The Panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not. (Recommendation type: Evidence-based and Panel consensus; benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Moderate)

Recommendation 1.2. Women with stage II or stage III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy. (Recommendation type: Evidence-based and Panel consensus; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Moderate)

Recommendation 1.3. Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy. (Recommendation type: Evidence-based and Panel consensus; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Moderate)

Recommendation 1.4. Women with stage I breast cancers not warranting chemotherapy should receive endocrine therapy but not receive ovarian suppression. (Recommendation type: Evidence-based; harms outweigh benefits; Evidence quality: High; Strength of Recommendation: Strong)

Recommendation 1.5. Women with node-negative cancers 1 cm or less (T1a, T1b) should receive endocrine therapy but not receive ovarian suppression. (Recommendation type: Evidence-based; harms outweigh benefits; Evidence quality: High; Strength of Recommendation: Strong)

Clinical Question 2

If ovarian suppression is recommended, should ovarian suppression be administered in combination with tamoxifen or an aromatase inhibitor (AI)?

Recommendation 2.1. The Panel recommends that ovarian suppression may be administered with either tamoxifen or an AI. (Recommendation type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)

Note from the National Guideline Clearinghouse (NGC) and the American Society of Clinical Oncology (ASCO): In 2014, ASCO performed a focused update of the 2010 guideline on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer to reflect emerging data on duration of tamoxifen treatment. The updated recommendations are presented below, followed by the recommendations from the 2010 guideline that remain unchanged.

2014 Recommendations

Clinical Question I

Which adjuvant endocrine treatments should be offered to women with hormone receptor–positive breast cancer who are pre- or perimenopausal? What is the appropriate duration?

Recommendation I. Women diagnosed with hormone receptor–positive breast cancer who are pre- or perimenopausal should be offered adjuvant endocrine therapy with:

Recommendation IA. Tamoxifen for an initial duration of 5 years (supported by 2010 evidence)

Recommendation IB. After 5 years, women should receive additional therapy based on menopausal status.

- Recommendation IB1. If women are pre- or perimenopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2013 evidence, see the Literature Review section of the focused update document).
- Recommendation IB2. If women have become definitively postmenopausal, they should be offered the choice of continuing tamoxifen for a total duration of 10 years or switching to up to 5 years of an aromatase inhibitor (AI), for a total duration of up to 10 years of adjuvant endocrine therapy. (Type: Evidence-based; Evidence quality for tamoxifen: High; Evidence quality for AI: High; Strength of recommendation: Strong; supported by 2010 and 2013 evidence)

Clinical Question II

Which adjuvant endocrine treatments should be offered to women with hormone receptor–positive breast cancer who are postmenopausal? What is the appropriate duration?

Recommendation II. Women diagnosed with hormone receptor–positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following initial options:

Recommendation IIA. Tamoxifen for a duration of 10 years. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2013 evidence); or

Recommendation IIB. An AI for a duration of 5 years. There are insufficient data currently to recommend an AI for a duration of greater than 5 years. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2010 evidence); or

Recommendation IIC. Tamoxifen for an initial duration of 5 years, then switching to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant endocrine therapy. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2010 evidence); or

Recommendation IID. Tamoxifen for a duration of 2 to 3 years and switching to an AI for up to 5 years, for a total duration of up to 7 to 8 years of adjuvant endocrine therapy. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2010 evidence)

Clinical Question III

What is the appropriate sequence of adjuvant endocrine therapy?

Recommendation III. Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered the alternative type of adjuvant endocrine therapy.

Recommendation IIIA. If women have received an AI but discontinued treatment at less than 5 years, they may be offered tamoxifen for a total of 5 years. (Type: Informal Consensus; Evidence quality: Low; Strength of recommendation: Weak; supported by 2010 evidence)

Recommendation IIIB. If women have received tamoxifen for 2 to 3 years, they should be offered the option of switching to an AI for up to 5 years, for a total duration of up to 7 to 8 years of adjuvant endocrine therapy. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2010 evidence)

Recommendation IV. Women who have received 5 years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment.

Recommendation IVA. If women are postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or the option of switching to up to 5 years of an AI, for a total duration of up to 10 years of adjuvant endocrine therapy. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2010 and 2013 evidence)

Recommendation IVB. If women are pre- or perimenopausal, or menopausal status cannot be ascertained, they should be offered 5 additional years of tamoxifen, for a total of 10 years of adjuvant endocrine therapy. (Type: Evidence-based; Evidence quality: High; Strength of recommendation: Strong; supported by 2013 evidence)

2010 Recommendations (No Changes)

2. Are there specific patient populations that derive differing degrees of benefit from an AI in comparison to tamoxifen?

Recommendation 2. Direct evidence from randomized trials does not identify a specific marker or clinical subset that predicted which adjuvant treatment strategy, tamoxifen or AI monotherapy or sequential therapy, would maximally improve outcomes for a given patient. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment.

The Update Committee recommends against using CYP2D6 genotype to select adjuvant endocrine therapy. The Update Committee encourages caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, fluoxetine; see Table 5 in the original guideline document) and tamoxifen because of the known drug-drug interactions.

3. What are the toxicities and risks of adjuvant endocrine therapy?

Recommendation 3. The Update Committee recommends that clinicians consider adverse effect profiles, patient preferences, and pre-existing conditions when recommending an adjuvant endocrine strategy for postmenopausal women. Clinicians should discuss adverse effect profiles when

presenting available treatment options to patients. The Update Committee suggests that clinicians consider recommending that patients change treatment if adverse effects are intolerable or if patients are persistently noncompliant with therapy.

5. Can the third-generation AIs be used interchangeably?

Recommendation 5. In the absence of direct comparisons, the Update Committee interprets available data as suggesting that benefits of AI therapy represent a "class effect." Meaningful clinical differences between the commercially available third-generation AIs have not been demonstrated to date. In the clinical opinion of the Update Committee (rather than direct evidence from randomized trials), post-menopausal patients intolerant of one AI but who are still candidates for adjuvant endocrine therapy may be advised to consider tamoxifen or a different AI.

Definitions

2014 and 2016 Focused Updates

Guide for Rating of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence-Based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement (see the "Availability of Companion Documents" field).
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the

Rating for Strength of Recommendation	Definition
Moderate	guideline's literature review and analyses) may also warrant a strong recommendation. There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

2010 Guideline

Not applicable

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hormone receptor–positive breast cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Prevention

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

2010 Guideline

To develop evidence-based guidelines, based on a systematic review, for endocrine therapy for postmenopausal women with hormone receptor–positive breast cancer

2014 Focused Update

To update the 2010 guideline on adjuvant endocrine therapy on the basis of emerging data on the optimal duration of treatment, particularly adjuvant tamoxifen

2016 Focused Update

To update the American Society of Clinical Oncology (ASCO) adjuvant endocrine therapy guideline based on emerging data concerning the benefits and risks of ovarian suppression in addition to standard adjuvant therapy in premenopausal women with estrogen receptor–positive breast cancer

Target Population

2010 Guideline

Postmenopausal women with hormone receptor–positive breast cancer

2014 Focused Update

Women with hormone receptor–positive breast cancer

2016 Focused Update

Premenopausal women with stage I to III hormone receptor–positive breast cancer

Interventions and Practices Considered

2010 Guideline and 2014 Focused Update

Adjuvant endocrine therapy:

- Use of a third-generation aromatase inhibitor (AI)
- Standard therapy with tamoxifen
- Combination therapy of tamoxifen and an AI

2016 Focused Update

Ovarian suppression in addition to adjuvant endocrine therapy for high-risk patients

Major Outcomes Considered

2010 Guideline

- Disease-free survival
- Overall survival
- Time to contralateral breast cancer
- Adverse effects of therapy
- Quality of life

2014 Focused Update

- Overall and/or disease-free survival, breast cancer-specific survival
- Time to recurrence
- Time to contralateral breast cancer

- Adverse events
- Health-related quality of life
- Rates of compliance

2016 Focused Update

- Outcomes of interest:
  - Overall survival (OS)
  - Disease-free survival (DFS)
  - Freedom from breast cancer at 5 years
  - Freedom from distant recurrence at 5 years
- Secondary outcomes of interest included:
  - Adverse events
  - Quality of life as measured by a validated, reliable instrument
  - Patient-reported outcomes
  - Cognitive impairment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2010 Guideline

Literature Search Strategy

The literature search for this update was facilitated by the systematic review completed by Cancer Care Ontario (CCO) that reviewed available literature through May 2007. American Society of Clinical Oncology (ASCO) guidelines staff conducted additional searches of the MEDLINE, PREMEDLINE, and Cochrane Collaboration Library electronic databases for published articles from May 2007 through February 2009 (for list of MEDLINE search terms, see the Appendix in the original guideline document). In addition, electronic databases for presentations, posters, and abstracts presented at the San Antonio Breast Cancer Symposium (SABCS) and ASCO Annual Meetings in 2007 and 2008 were searched. Additional sources were identified by hand-searching bibliographies of relevant articles. Search terms included all the agents under consideration ("tamoxifen," "anastrozole," "exemestane," "letrozole," and "aromatase inhibitors") along with identified brand names (including European and North American versions). These terms were combined with the disease terminology "breast neoplasms," "carcinoma," "adenocarcinoma," and "tumor." The search was limited to phase III randomized, controlled trials; meta-analyses; systematic reviews; and existing practice guidelines. Other trial designs, including phase I or II trials and either prospective or retrospective cohort studies, were excluded. English-language studies available in full text and published in peer-reviewed journals were included. Following the Update Committee meeting, ASCO staff searched the programs for ASCO's 2009 Annual Meeting and the 2009 SABCS meeting to include updated data from the trials described therein.

Inclusion and Exclusion Criteria

Articles identified for inclusion in this systematic review met the following criteria: (1) the intervention was for the adjuvant therapy of breast cancer, (2) participants were randomly assigned to any of the treatments described previously, and (3) reports included at least one of the following primary outcomes of interest: overall survival, disease-free survival, or breast cancer-specific survival. Three different treatment strategies were identified on the basis of the timing of aromatase inhibitor (AI) therapy: initial endocrine therapy (hereafter referred to as a primary adjuvant strategy), sequential therapy with treatment divergence if the patient was disease-free following 1 to 4 years of initial treatment with adjuvant endocrine agents (most often tamoxifen), or extended therapy with random assignment if the patient was disease-free following 5 years of treatment with adjuvant tamoxifen. Trials that used earlier generations of AIs, included neoadjuvant therapy, reported laboratory but not primary

disease-related outcomes of interest, or were not randomized were excluded. Trials that treated patients with metastatic breast cancer were also excluded.

2014 Focused Update

Literature Search Strategy

The MEDLINE database (PubMed: [date range: 2009/01/01 to 2013/03/04]) was searched for evidence reporting on outcomes of interest. SABCS and ASCO conference proceedings were searched: SABCS for 2011, 2012; and ASCO for 2011, 2012, and 2013. Reference lists from seminal papers and recent review articles were scanned for additional citations. The literature search strategy and search results are available in Data Supplements 2 and 3 respectively (see the "Availability of Companion Documents" field).

Because this update addressed a question not specifically identified in previous updates, the search date parameters were broadened to find historical trials.

Articles were selected for inclusion in the systematic review of the evidence if they were

- Published journal articles from the medical literature
- Phase III randomized controlled trials
- Meeting abstracts, if presentations or posters were available
- Written language: English only
- Systematic reviews with or without meta-analysis
- Study population: female

Articles were excluded from the systematic review if they were (1) other reviews (consensus, narrative, expert panel, guidelines); (2) editorials, commentaries, letters, news articles, case reports; or (3) published in a non-English language.

2016 Focused Update

Literature Search Strategy

PubMed was searched on June 24, 2015 for evidence (1966 - June 24, 2015) reporting on outcomes of interest using the keywords "breast cancer," "ovarian function suppression, "tamoxifen," and "aromatase inhibitor" and were reviewed for terms relating to hormone receptor status, premenopausal status, publication type, and study design. Reference lists from seminal papers and recent review articles were scanned for additional citations, and known updates of included evidence were obtained as available. The literature search strategy used in the PubMed database is available in the Data Supplement (see the "Availability of Companion Documents" field).

Study Selection Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published reports of:

- Systematic reviews (with or without meta-analysis)
- Randomized controlled trials (phase II or III)

that reported on the following interventions:

- Endocrine therapies, including:
    - Selective estrogen receptor modulators (tamoxifen)
    - Nonsteroidal third-generation AIs (e.g., anastrozole)
    - Steroidal third-generation AI (exemestane)
- Ovarian suppression, including:
    - Luteinizing hormone–releasing hormone analogs (goserelin)
    - GnRH (triptorelin)
    - Surgical ablation (bilateral oophorectomy)
    - Bilateral ovarian irradiation

that reported on the following outcomes of interest:

- Overall survival (OS)
- Disease-free survival (DFS)

- Freedom from breast cancer at 5 years
- Freedom from distant recurrence at 5 years
- Secondary outcomes of interest included:
    - Adverse events
    - Quality of life as measured by a validated, reliable instrument
    - Patient-reported outcomes
    - Cognitive impairment

Articles were excluded from the systematic review if they were:

- Noncomparative studies
- Meeting abstracts not subsequently published in peer-reviewed journals
- Published in a non-English language

Number of Source Documents

2010 Guideline

Twelve prospective, randomized clinical trials originally identified by the co-chairs were the focus of this systematic review. Four meta-analyses identified from the search were also considered.

2014 Focused Update

6 papers and 1 presentation (from 5 trials) met selection criteria and underwent data abstraction.

2016 Focused Update

4 trials met selection criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

2010 Guideline

Not applicable

2014 and 2016 Focused Updates

Guide for Rating of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

2010 Guideline

Data Extraction

Reports and publications that met inclusion criteria were identified in a first round of review by members of the American Society of Clinical Oncology (ASCO) staff. The Update Committee co-chairs subsequently reviewed the list of articles, and staff obtained full-text copies of papers that satisfied the inclusion criteria. ASCO staff completed full-text review of these articles, including assessment of inclusion and exclusion criteria. Articles that provisionally met inclusion criteria underwent data extraction for patient characteristics, study design and quality, interventions, outcomes, and adverse events. Evidence summary tables were reviewed for accuracy and completeness by an ASCO staff member who was not involved in their original preparation.

2014 Focused Update

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by an ASCO staff member in consultation with the Update Committee co-chairs. Data were extracted by one ASCO staff member and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the co-chairs, if necessary.

2016 Focused Update

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by an ASCO staff member in consultation with the Co-Chairs. Data were extracted by one ASCO staff member and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2010 Guideline

The American Society of Clinical Oncology (ASCO) Guideline Update Panel reconvened to develop an update. The ASCO technology assessment in 2004 on the use of aromatase inhibitors (AIs) in the adjuvant setting identified multiple unanswered questions regarding optimal endocrine treatment for postmenopausal women. New data on these remaining questions formed the foundation for this guideline update. The Update Committee focused on the optimal adjuvant endocrine strategy with use of either tamoxifen, AIs, or both in sequence; the appropriate duration of AI therapy; the long-term adverse effects of AI therapy; identification of subpopulations who might derive selective benefit from either AI- or tamoxifen-based treatments; efficacy of AIs among premenopausal women; and similarities or differences among commercially available third-generation AIs.

Consensus Development Based on Evidence

The Update Committee met twice, first in San Antonio in December 2008 and again at ASCO Headquarters in April 2009. The Update Committee was charged with updating the clinical questions, reviewing evidence collected from the systematic review, and drafting the new recommendations. Additional work on the guideline was primarily completed by the co-chairs and ASCO staff. The draft guideline document was developed by the co-chairs and ASCO staff and reviewed by the entire Update Committee.

2014 Focused Update

Update Committee Composition

To address the clinical question, an Update Committee with multidisciplinary representation in medical oncology, community oncology, patient representation, implementation, and guideline methodology was convened. The Update Committee was led by two co-chairs who had the primary responsibility for the development and timely completion of the guideline. The Update Committee members are listed in Appendix Table AI (online only [see the "Availability of Companion Documents" field]).

Guideline Development Process

The Update Committee met on several occasions and corresponded through email; progress on guideline development was driven primarily by the Update Committee along with ASCO staff. The purpose of the Committee meetings was for members to contribute content provide critical review, interpret evidence, and finalize the guideline recommendations based upon the consideration of the evidence. All members of the Update Committee participated in the preparation of the draft guideline document.

Development of Recommendations

The guideline recommendations were crafted, in part, using the GuideLines Into DEcision (GLIDES) methodology and accompanying BRIDGE-Wiz™ software (http://medicine.yale.edu/cmi/glides/index.aspx). This method helps guideline panels systematically develop clear, translatable, and implementable recommendations using natural language, based on the evidence and assessment of its quality to increase usability for end users. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Panel focus the discussion, avoid using unnecessary and/or ambiguous language and clearly state its intentions.

2016 Focused Update

Guideline Update Development Process

The Update Panel met in person and/or webinar and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Update Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

The guideline recommendations are crafted, in part, using the GLIDES methodology. In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (see Methodology Supplement for more information; see the "Availability of Companion Documents" field).

Detailed information about the methods used to develop this update is available in the guidelines Methodology Supplement on the ASCO Web site, including an overview (e.g., panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process, and quality assessment.

Rating Scheme for the Strength of the Recommendations

2010 Guideline

Not applicable

2014 and 2016 Focused Updates

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence-Based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current

Type of Recommendation	Definition
	guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement (see the "Availability of Companion Documents" field).
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

2010 Guideline

Per standard American Society of Clinical Oncology (ASCO) practice, the guideline was submitted to the *Journal of Clinical Oncology* for peer review. The content of the guideline was reviewed and approved by both the ASCO Clinical Practice Guideline Committee and the Board of Directors before publication.

2014 Focused Update

The draft guideline document was disseminated for external review and submitted to the *Journal of Clinical Oncology* for peer review and publication. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee prior to publication.

The Clinical Practice Guideline Committee approved this focused review on January 31, 2014.

2016 Focused Update

The penultimate version of the guideline was circulated for external review and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Update Panel and the ASCO Clinical Practice Guideline Committee before publication.

The Clinical Practice Guideline Committee approved this focused update on November 30, 2015.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

2010 Guideline

The recommendations are based on 12 randomized controlled trials and 4 meta-analyses. Refer to the "Literature update and discussion" sections in the original guideline document (see the "Availability of Companion Documents" field) for specific evidence for each recommendation.

2014 Focused Update

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

2016 Focused Update

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

2010 Guideline

An adjuvant treatment strategy incorporating an aromatase inhibitor (AI) as primary (initial endocrine therapy), sequential (using both tamoxifen and an AI in either order), or extended (AI after 5 years of tamoxifen) therapy reduces the risk of breast cancer recurrence compared with 5 years of tamoxifen alone. Data suggest that including an AI as primary monotherapy or as sequential treatment after 2 to 3 years of tamoxifen yields similar outcomes.

2014 Focused Update

Appropriate management of women with hormone receptor–positive breast cancer, resulting in increased overall survival (OS) and distant disease-free survival (DFS), reduced breast cancer–specific mortality, decreased risk of recurrence, decreased risk of contralateral breast cancer

2016 Focused Update

Appropriate administration of ovarian suppression in combination with tamoxifen or an aromatase AI

Potential Harms

2010 Guideline

- The Update Committee encourages caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, fluoxetine) and tamoxifen because of the known drug-drug interactions.
- Appendix Tables A4 through A8 in the original guideline document (see the "Availability of Companion Documents" field) include an abbreviated list of the adverse effects tabulated from the therapies evaluated in the prospective, randomized trials discussed. Four main categories of symptoms are detailed: cardiovascular, musculoskeletal, gynecologic, and climacteric.

2014 Focused Update

Women receiving extended adjuvant endocrine therapy are at risk for ongoing adverse effects, such as menopausal symptoms, and less common, but more serious, adverse effects. Tamoxifen is associated with risks of thromboembolism and uterine cancer. Aromatase inhibitors (AIs) are associated with ongoing risk of osteoporosis. Clinicians should monitor patients for sequelae of treatment according to established guidelines. Table 3 in the focused update document provides an abbreviated list of the adverse effects tabulated from the therapies evaluated in the prospective, randomized trials discussed.

2016 Focused Update

Potential harms include worse menopausal symptoms and sexual functioning, including hot flashes, sweating, weight gain, vaginal dryness, decreased libido, and osteopenia/osteoporosis. The Panel recommended strongly that the clinical and adverse effect profile issues should be discussed with patients when choosing whether to add either tamoxifen or an AI to ovarian suppression.

Contraindications

Contraindications

2010 Guideline

Aromatase inhibitors (AIs) are contraindicated in premenopausal women.

2014 and 2016 Focused Updates

Not applicable

Qualifying Statements

Qualifying Statements

2010 Guideline

- The American Society of Clinical Oncology's (ASCO's) practice guidelines reflect expert consensus based on clinical evidence and literature available at the time they are written and are intended to assist physicians in clinical decision making and to identify questions and settings for further research. Because of the rapid flow of scientific information in oncology, new evidence may have emerged since the guideline was submitted for publication. Guidelines and assessments are not continually updated and may not reflect the most recent evidence. Guidelines address only the topics specifically identified in the guideline and are not applicable to interventions, disease, or stages of disease not specifically identified. Guidelines cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. ASCO guidelines describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO's guidelines, or for any errors or omissions.
- Several important limitations of the existing literature were identified. Of particular note is the timing of random assignment (see Figure 1 in the original guideline document). Most of the sequential trials and all the extended trials randomly assigned women who were free of recurrence through multiple years of tamoxifen therapy, effectively excluding women with early recurrence. For this reason, the patient populations in the sequential and extended trials may differ importantly from one another and from those patients in the primary therapy studies. Another limitation is the relatively short follow-up time. Post-menopausal breast cancer is a disease with a long natural history, and disease recurrence decades after diagnosis is not uncommon. The longest available median follow-up in the trials included here is slightly more than 8 years; most studies have considerably shorter follow-up. For the majority of the efficacy outcomes across all studies, the median time to event has yet to be reached. The relatively modest number of events may also limit study conclusions.

2014 Focused Update

- The clinical practice guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information therein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis, and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.
- Limitations of the studies discussed in the focused update include differing amounts of median follow-up and the fact that the studies were performed in different eras, in part resulting in insufficient information to appraise the quality of three of the studies. Some of the populations in these studies did not have hormone receptor–positive breast cancer and/or their hormone receptor status was unknown. In addition, there are relatively few new data on adverse events for those who have received adjuvant tamoxifen for more than 5 years. The studies in the focused update provided insufficient data on adverse effects, especially climacteric and/or sexual adverse effects. Evidence on a broader set of adverse events could affect women's risk-benefit perceptions and willingness to take tamoxifen for more than 5 years, perhaps modulated by age and menopausal status. The studies did not report on and/or did not measure health-related quality of life; at the time of the development of this guideline, results by menopausal status were not available, and there are few data on extended durations of aromatase inhibitors (AIs).

2016 Focused Update

Limitations of the included trials are discussed throughout the manuscript. Methodologic shortcomings include open-label designs, poor accrual and early closure of E-3193, and the lower than expected event rates in TEXT and SOFT leading to diminished statistical power. Furthermore, data based on unplanned subset analyses are often inflated, with unknown error rates, making interpretation difficult. There is also a lack of survival data. Nonetheless, the Panel consulted the current available evidence and through consensus and clinical experience developed the recommendations.

Implementation of the Guideline

Description of Implementation Strategy

2010 Guideline

An implementation strategy was not provided.

2014 and 2016 Focused Updates

American Society of Clinical Oncology (ASCO) guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and cancer survivors, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update on ovarian suppression. J Clin Oncol. 2016 May 10;34(14):1689-701. [19 references] PubMed

Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Malin J, Mamounas EP, Rowden D, Solky AJ, Sowers MR, Stearns V, Winer EP, Somerfield MR, Griggs JJ, American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol. 2010 Aug 10;28(23):3784-96. [124 references] PubMed

Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Rowden D, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol. 2014 Jul 20;32(21):2255-69. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 Aug 10; addenda released 2014 Jul 20 and 2016 May 10

Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

Source(s) of Funding

American Society of Clinical Oncology

Guideline Committee

American Society of Clinical Oncology (ASCO) Practice Guidelines Update Committee

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2010 Guideline

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2014 Focused Update

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2016 Focused Update

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Financial Disclosures/Conflicts of Interest

2010 Guideline

The Update Committee was assembled in accordance with American Society of Clinical Oncology's (ASCO's) Conflict of Interest Management Procedures for Clinical Practice Guidelines. Members completed ASCO's disclosure form, which requires disclosure of financial and other interests relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Expert Testimony: None

Other Remuneration: None

2014 Focused Update

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Expert Testimony: None

Patents, Royalties, and Licenses: None

Other Remuneration: None

2016 Focused Update

Panel Formation and Conflicts of Interest

A multidisciplinary expert Panel was formed and tasked with updating the Adjuvant Endocrine Therapy for Women with Hormone Receptor–Positive Breast Cancer guideline. Panel members had expertise in breast oncology and community oncology and included a patient representative (Appendix Table A1 , online only). The Update Panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines (procedures are summarized at http://www.asco.org/rwc). Members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Procedures, the majority of the members of the Update Panel did not disclose any such relationships.

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated.

Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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No relationship to disclose

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

2010 Guideline

Available from the American Society of Clinical Oncology (ASCO) Web site.

2014 Focused Update

Available from the Journal of Clinical Oncology Web site.

2016 Focused Update

Available from the Journal of Clinical Oncology Web site.

Availability of Companion Documents

The following are available:

- American Society of Clinical Oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone-receptor positive breast cancer. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2010. 19 p. Slide set. Available from the American Society of Clinical Oncology (ASCO) Web site.
- American Society of Clinical Oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. Guideline summary. J Oncol Pract. 2010;6(5):243-6. Available from the Journal of Oncology Practice Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2014. 8 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. Data supplement. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2014. 12 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. Clinical practice guideline update. Slide set. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2014. 21 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. Summary of recommendations table. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2014. 3 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. Methods supplement. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2016. 5 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. Data supplement. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2016. 7 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update. Slide set. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2016. 13 p. Available from the ASCO Web site.
- Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update. Summary of recommendations table. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2016. 2 p. Available from the ASCO Web site.

Patient Resources

The following are available:

- Decision aid tool. Adjuvant endocrine therapy for hormone receptor-positive breast cancer. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2010. 8 p. Available from the American Society of Clinical Oncology (ASCO) Web site.
- Hormonal therapy for early-stage hormone receptor-positive breast cancer. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2016 Feb 16. Available from the ASCO Web site.

NGC Status

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